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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/919,143	07/31/2001	Leandro Christmann	AVI 008	2824

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/919,143	CHRISTMANN, LEANDRO	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4-12-04*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *10/05/04*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-50 have been canceled. Claims 51-82 have been added.

Claim Rejections - 35 USC § 112

Claims 21 and 36-50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The previous new matter rejections have been withdrawn because the claims have been canceled.

The phrase "microinjection assembly comprising an optical microscope and a micropipette" in claims 51, 65 and 74 is new matter. Applicants point to original claim 8, which requires "providing a microinjection assembly comprising an optical microscope having an objective with an optical axis, a microinjection system comprising a micropipette operably connected to a micromanipulator and an oscillator and an oblique macro-monitoring system." As originally filed, it appears that the following items were provided: 1) a microinjection assembly (comprising an optical microscope), 2) a microinjection system (comprising a micropipette), 3) an oscillator and 4) an oblique macro-monitoring system. It is not readily apparent that the microinjection assembly in claim 8 as originally filed comprised 1) an optical microscope and 2) a micropipette as newly claimed.

The phrase "viewing the micropipette from an angle oblique to the surface of an embryo" in claim 51 does not have support on pg 23, line 3-6, which states the microinjection assembly comprises an obliquely angled macro monitoring unit (with a macro lens) having an optical axis directed to the object at an angle oblique to the surface of the object. The specification states the surface of the object is viewed from an oblique angle; the micropipette is not viewed from an oblique angle as claimed. As drawn in Fig. 1 and described on pg 23, lines 3-6, the angle of the micropipette may be perpendicular to the angle of the macro monitoring unit, which is not "oblique" (see definition of oblique Merriam-Webster Online ("neither perpendicular nor parallel"), attached).

The phrase "wherein the embryo is placed in an incident light beam angled from an optical axis of the objective" in claims 53, 66 and 75 has support on pg 25, lines 9-11, which describes the microinjection system has "an incident beam of light [that] is angled from the optical axis 6 of the objective 2" in view of Fig. 1. (Claim 8, step d, as originally filed does not support the phrase because it requires "positioning the micropipette by monitoring the position of the micropipette relative to the avian embryo by the oblique macro monitoring system." It is not readily apparent where the "incident light beam" is in relation to the "optical axis of the objective" from claim 8, step d, or Fig. 1.)

The phrase "wherein the microinjection assembly comprises a piezo-electric oscillator" in claim 55 does not have support on pg 22, line 9, which teaches the microinjection system 100 further comprises a piezo-electric oscillator. As originally

filed, the microinjection system and microinjection assembly had different scopes. Therefore, the specification as originally filed did not contemplate the scope of a microinjection assembly further comprising the piezo-electric oscillator as newly claimed.

The phrase "viewing the micropipette from an angle less than 90 degrees from perpendicular to an embryo" does not have support in the specification as originally filed (claim 65). Pg 23, line 3-6, states the microinjection assembly comprises an obliquely angled macro-monitoring unit (with a macro lens) having an optical axis directed to the object at an angle oblique to the surface of the object. The specification states the surface of the object is viewed from an oblique angle; the micropipette is not viewed from less than 90 degrees from perpendicular to an embryo (an oblique angle) as claimed.

The phrase "viewing the micropipette from the side" in claim 74 does not have support in Fig. 1, 2a, 2b or 2c, as originally filed. "From the side" encompasses more than pg 23, lines 3-6, Fig. 1 and Fig. 2, because it would include viewing the micropipette as it is inserted into the embryo at a parallel angle. This breadth is not readily apparent from any of the Figures or the specification as originally filed. In addition, none of the specification contemplates the angle at which the micropipette is viewed. The oblique angles mentioned in the specification are attempting to describe the angle at which the surface of the embryo is viewed. Therefore, "viewing the micropipette from the side" does not have support in the specification as originally filed.

Claims 51-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a transgenic avian by 1) providing i) an optical microscope having an objective, ii) a micropipette, iii) a monitoring unit and iv) a chicken embryo, wherein the optical axis of the monitoring unit (62, in Fig. 1, see pg 23, lines 3-6) is at an oblique angle to the optical axis of the objective (6, in Fig. 1, see pg 25, line 11), 2) injecting a nucleic acid sequence into the avian embryo using the micropipette; and 3) allowing the avian embryo to develop into a transgenic avian that is a germline chimera, does not reasonably provide enablement for making any species of transgenic avian or applying oscillation or piezo-electric oscillation to the micropipette used to deliver the nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection of claims 21 and 36-50 under enablement has been withdrawn because the claims have been canceled.

The broad claims are directed toward delivering nucleic acid into an avian embryo to produce a transgenic avian. The only enabled purpose for the method is to obtain a transgenic avian that is a germline chimera, i.e. that carries the exogenous nucleic acid in its germ cells and passes the nucleic acid on to its offspring. The broad claims encompass delivering nucleic acids in the form of vector (plasmids, viral vectors), cells transfected with a vector or a donor nucleus. Methods of making transgenic chickens by injecting vectors or cells transfected with vectors into chicken embryos were known in the art:

PGCs had been isolated from chickens, transduced with retrovirus, and immediately injected into the vasculature of Stage 15 chick embryos to obtain germline transmission of a transgene (Vick, Proc. R. Soc. Lond., 1993, Vol. 251, pg 179-182). Plasmid DNA had been injected into the germinal disc of chick zygotes isolated before being laid to obtain germline transmission of a transgene (Love, of record, Bio/Technology, 1994, Vol. 12, pg 60-63). Retroviral vectors had been injected into the subgerminal cavity of an avian embryo in a freshly laid egg to obtain germline transmission of a transgene (Thoroval, Transgenic Research, 1995, Vol. 4, pg 369-376). Retroviral vectors had been used to introduce a truncated antibody receptor into chickens "somatically" and express the receptor in the bursa at hatch (Sayegh, Dec. 15, 1999, Vol. 72, pg 31-37; pg 32, 2nd full ¶, lines 2-5 and 16-18; ¶ bridging pg 33-34).

The specification does not enable making any transgenic avian as broadly encompassed by claims 51, 65 and 74. The specification summarizes methods of introducing a nucleic acid into chicken embryos known in the art (pg 3-5). The specification summarizes methods of obtaining transgenic mice known in the art at the time of filing (pg 2-3); however, methods of making transgenic mice do not correlate to making transgenic avians (Proudman of record, 2001, "The quest for transgenic poultry: birds are not mice with feathers" Biotechnology in Animal Husbandry, Vol. 5, Kluwer Academic Publishers, pg 283-299). The specification does not enable injecting obtaining any transgenic germline chimeric avian because the art at the time of filing was limited to using the method to obtain germline chimeric chickens. The specification does not correlate the structure of chicken embryos to any other avian embryos. The

art did not teach obtaining a germline chimeric non-chicken avian. Without such guidance it would require one of skill undue experimentation to introduce a nucleic acid into any species of avian embryo such that a germline chimeric avian was obtained. The claims should be limited to chickens as in claim 59, 70 and 79.

Applicants argue the invention provides an improved method of injecting nucleic acid into an avian germinal disc or embryo. Applicants argue the methods are improved over other such methods known in the art. Therefore, applicants conclude, the practitioner could produce transgenic avians other than transgenic chickens (pg 8). Applicants' argument is not persuasive. The facts set forth do not allow one to reasonably come to such a conclusion. While a nucleic acid could be injected into any avian embryo, the only transgenics avians (which must be germline chimeras according to the instant application) made by injecting a nucleic acid into an embryo known in the art were chickens. It is not apparent why transgenic non-chicken avians had not been made in the art. Thus, it is not readily apparent that any purported improvements in how the nucleic acid is injected would allow one of skill to overcome the unpredictability in the art and suddenly be able to inject a nucleic acid into any avian embryo and obtain a germline chimera. Without some indication that the problem with injecting a nucleic acid into any avian embryo and obtaining a germline chimera was the "optically opaque yolk underlying the oocyte or germinal disk", applicants' improvement would not be enough for one of skill to predictably inject a nucleic acid into any avian embryo to obtain any transgenic avian as broadly claimed.

Claims 54, 55, 67 and 76 require using a micropipette that has an oscillator, specifically a piezo-electric oscillator, which was only used in the art of transgenics for delivering a donor nucleus (Dozortsev, of record, Zygote, May 1998, Vol. 6, No. 2, pg 143-147, and Korfiatis, of record, Cloning and Stem cells, 2001, Vol. 3, No. 3, pg 125-138, for example). Therefore, claims 54, 55, 67 and 76 are limited to methods of delivering a donor nucleus to an avian embryo. Claims 54, 55, 67 and 76 are not enabled because the specification does not enable delivering a donor nucleus to make a transgenic avian. The specification contemplates removing the nucleus of an avian egg (pg 37, Example 3) and transplanting a donor nucleus into the egg (pg 39, Examples 5 and 6), i.e. cloning. The art at the time of filing did not teach how to clone avians. Therefore, it was unpredictable how to clone avians at the time of filing. The specification does not teach obtaining a viable offspring by delivering a donor nucleus. The specification does not adequately correlate methods known in the art capable of cloning to the method of microinjection described in the specification. The specification does not correlate the structure of mammalian embryos capable of cloning known in the art to avians embryos such that one of skill could use mammalian cloning methods to clone avians. Without such guidance it would require one of skill undue experimentation to microinject a donor nucleus using oscillation to make transgenic avians that carry the donor nucleus. Therefore, claims 54, 55, 67 and 76 are not enabled as they relate to using oscillation to deliver a donor nucleus to make a transgenic avian.

Applicants argue an oscillator is used to produce micropipette oscillations when injecting nucleic acid into an embryo of an avian in accordance with the invention (¶ bridging pg 8-9). Applicants' argument is not persuasive because according to the art of record, using an oscillating pipette is limited to delivering a donor nucleus for cloning.

Claims 51-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 21 and 36-50 has been withdrawn because the claims have been canceled.

The metes and bounds of a "microinjection assembly" in claims 51, 65 and 74 cannot be determined. It is unclear if the metes and bounds of a "microinjection assembly" are limited to the microinjector portion of Fig. 1, if it encompasses only the optical microscope and microinjector in Fig. 1, or if it encompasses the optical microscope, the microinjector and the monitor described in Fig. 1. Clarification is required.

The phrase "an angle oblique to the surface of an embryo" is indefinite (claim 51). The embryo has a surface of 360°. Therefore, the angle oblique relative to any surface on the embryo is any angle. It is unclear how the phrase is intended to limit the angle at which the micropipette is viewed.

The phrase "injecting nucleic acid" in claims 51, 65 and 74 is indefinite. One nucleic acid does not have any function without being in a sequence of nucleic acids;

therefore, injecting one nucleic acid into an embryo as claimed has no purpose in the instant application. The claims should be limited to injecting a nucleic acid sequence as on pg 12, lines 3-4.

The phrase "wherein the embryo is placed in an incident light beam angled from an optical axis of the objective" in claims 53, 66 and 75 is indefinite. The metes and bounds of what applicants consider "incident" light cannot be determined. An embryo placed in a light beam "angled from" the optical axis does not make sense. Overall, the placement of the embryo relative to the light beam and optical axis is not clearly set forth.

The phrase "wherein the avian embryo is an embryo of a chicken" (claims 59, 70 and 79) should be "wherein the avian embryo is a chicken embryo" to be more clear.

The phrase "comprising delivering the embryo to a recipient avian female" (claim 60, 71 and 80) should be "further comprising delivering the avian embryo to a recipient avian female" to be more clear.

The phrase "through the pipette" in claim 62, 72 and 81 and lacks antecedent basis in the parent claims.

The phrase "the germinal disc" in claims 62, 63, 72 and 81 lacks antecedent basis in the parent claims because the embryo may no longer have a germinal disc.

Claim 64 does not further limit claim 51. If the nucleic acid is injected into the embryo as in claim 51, it comes into contact with the cells of the embryo and is thereby "delivered to a recipient cell in the avian embryo" as in claim 64. Thus, the phrase in

claim 64 does not further limit claim 51 in any way as written. Likewise, claims 73 and 82 do not further limit claims 65 and 74.

The metes and bounds of the phrase "viewing the micropipette from an angle less than 90 degrees from perpendicular to an embryo" are indefinite (claim 65). Comparing the angle at which the micropipette is viewed relative to any embryo does not make sense in context of the specification which describes the angle at which the micropipette and the macro-monitoring unit relative to the embryo in the optical axis of a microscope (pg 7, lines 8-12, taken with pg 25, lines 9-11 and Fig. 1).

The metes and bounds of the phrase "viewing the micropipette from the side" in claim 74 is indefinite. It is unclear if "from the side" means relative to the micropipette or to the microinjection assembly as a whole. It is unclear if viewing the micropipette "from the side" while it is at an angle that is parallel to the optical axis of the microscope is encompassed by the claim (a micropipette injected at an angle parallel to the optical axis of the microscope can still be seen by the microscope).

Claim Rejections - 35 USC § 103

Claims 51-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka (1994, J. Reprod. Fert., Vol. 100, pg 447-449) in view of Sang (Molecular Reproduction and Development, 1989, Vol. 1, pg 98-106).

The rejection of claims 21 and 36-50 has been withdrawn because the claims have been canceled.

Tanaka (1994, J. Reprod. Fert., Vol. 100, pg 447-449) taught delivering the zygote into the birth canal of a hen and allowing the zygote to become a chick (pg 447, col. 2, "Materials and Methods;" pg 448, Fig. 1; pg 448, col. 1, line 4; pg 448, col. 2, 1st full ¶, line 9). Tanaka taught delivering DNA to the zygote before delivering the zygote to the recipient hen (pg 449, col. 1, last ¶). Tanaka did not teach delivering the DNA to the zygote with a microscope and a micropipette as claimed.

However, Sang (Molecular Reproduction and Development, 1989, Vol. 1, pg 98-106) taught delivering DNA to a chicken zygote using a micropipette held in a micromanipulator and allowing the zygote to become a chick (pg 99, col. 1).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to deliver DNA to a zygote, deliver the zygote into a recipient female and allow the zygote to become a chick as taught by Tanaka wherein the DNA was delivered using the micromanipulator taught by Sang. One of ordinary skill in the art at the time the invention was made would have been motivated to deliver the DNA of Tanaka using the micromanipulator taught by Sang because Sang had increased survival rate as compared to Tanaka (pg 100, lines 1-2, of Sang as compared to the last ¶ of Tanaka).

The micropipette held in a micromanipulator taught by Sang on pg 99, col. 1, 2nd full ¶) inherently has a microscope because a micromanipulator is an attachment for a microscope (see definitions of "micromanipulator" by Dorlands Medical Dictionary and by Drug Discovery and Development). For Sang to determine the DNA was inserted at

a depth of 140-200 μm beneath the vitelline membrane (pg 99, col. 1, 2nd full ¶, 1st sentence), the embryo must have been monitored by a microscope as claimed.

A zygote is an embryo because it is an organism in the early stages of development (see definition of "embryo" by Stedman's Medical Dictionary). In addition, a zygote is an embryo because Tanaka, one of ordinary skill in the art at the time the invention was made, referred to the one-cell fertilized ovum as an embryo (last ¶).

Sang did not teach how the embryo was viewed or the angle at which the micropipette was injected to the embryo relative to how the embryo was viewed. However, if the micropipette was being inserted into the embryo at an angle parallel to the optical axis of the microscope, the side of the micropipette was visible from the optical axis of the microscope. Viewing the side of the micropipette as it is being inserted into the embryo while the microscope is being inserted parallel to the optical axis of the microscope is equivalent to monitoring the micropipette from an angle that is oblique to the optical axis of the objective and the axis of the micropipette. If the micropipette was inserted into the embryo at an angle oblique to the optical axis of the microscope, the side of the micropipette was monitored from an angle that is oblique to the optical axis of the objective and to the axis of the micropipette.

Thus, Applicants' claimed invention, as a whole is prima facie obvious in the absence of evidence to the contrary.

Applicants argue the microinjection assembly of Sang allows the operator to view the micropipette from above. Therefore, applicants conclude the rejection is misplaced. Applicants' argument is not persuasive. If applicants are attempting to require

observing the micropipette from an angle oblique to a line drawn from the embryo to the center of the earth, Sang meets the limitation because Sang did not look down the center of the shaft of the micropipette. The microscope would not look down the micropipette shaft. Therefore, the microscope inherently viewed the side of the micropipette from an angle that is oblique to a line drawn from the embryo to the center of the earth (although slight). Drawing a line from the edge of embryo to the center of the earth also would provide a more oblique angle at which the embryo is viewed. Overall, it is cannot be determined how to overcome the obviousness rejection while describing the angle at which the micropipette is viewed as described in Fig. 1.

Double Patenting

The objection of claim 36 under 37 CFR 1.75 as being a substantial duplicate of claim 21 has been withdrawn because the claims have been canceled.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
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